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Hunting for origins of migraine pain: Cluster analysis of spontaneous and capsaicin-induced firing in meningeal trigeminal nerve fibers

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Abstract

© 2015 Zakharov, Vitale, Kilinc, Koroleva, Fayuk, Shelukhina, Naumenko, Skorinkin, Khazipov and Giniatullin. Trigeminal nerves in meninges are implicated in generation of nociceptive firing underlying migraine pain. However, the neurochemical mechanisms of nociceptive firing in meningeal trigeminal nerves are little understood. In this study, using suction electrode recordings from peripheral branches of the trigeminal nerve in isolated rat meninges, we analyzed spontaneous and capsaicin-induced orthodromic spiking activity. In control, biphasic single spikes with variable amplitude and shapes were observed. Application of the transient receptor potential vanilloid 1 (TRPV1) agonist capsaicin to meninges dramatically increased firing whereas the amplitudes and shapes of spikes remained essentially unchanged. This effect was antagonized by the specific TRPV1 antagonist capsazepine. Using the clustering approach, several groups of uniform spikes (clusters) were identified. The clustering approach combined with capsaicin application allowed us to detect and to distinguish “responder” (65%) from “non-responder” clusters (35%). Notably, responders fired spikes at frequencies exceeding 10 Hz, high enough to provide postsynaptic temporal summation of excitation at brainstem and spinal cord level. Almost all spikes were suppressed by tetrodotoxin (TTX) suggesting an involvement of the TTX-sensitive sodium channels in nociceptive signaling at the peripheral branches of trigeminal neurons. Our analysis also identified transient (desensitizing) and long-lasting (slowly desensitizing) responses to the continuous application of capsaicin. Thus, the persistent activation of nociceptors in capsaicin-sensitive nerve fibers shown here may be involved in trigeminal pain signaling and plasticity along with the release of migraine-related neuropeptides from TRPV1 positive neurons. Furthermore, cluster analysis could be widely used to characterize the temporal and neurochemical profiles of other pain transducers likely implicated in migraine.

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Keywords

Capsaicin, Cluster analysis, Pain, Spike, Trigeminal nerve